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Extraintestinal Manifestations of Pediatric Inflammatory Bowel Disease: Prevalence, Presentation and anti-TNF Treatment

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ABSTRACT

Background: There is a paucity of data on extraintestinal manifestations (EIM) and their treatment in pediatric patients with inflammatory bowel disease (IBD).

Methods: Since 2008, the Pediatric Swiss IBD Cohort Study has collected data on the pediatric IBD population in Switzerland. Data on 329 patients were analyzed retrospectively.

Results: 55 patients (16.7%) suffered from 1-4 EIM (39 Crohn`s disease, 12 ulcerative colitis and 4 IBD-Unclassified (IBD-U) patients). At IBD onset, presence of EIM was more frequent than in the adult population (8.5% vs. 5.0%, p=0.014). EIM were more frequent in CD when compared to UC/IBD-U (22.5 vs. 10.3%, p=0.003). The most prevalent EIM were peripheral arthritis (26/329, 7.9%) and aphthous stomatitis (24/329, 7.3%). 27.6% of all EIM appeared before IBD diagnosis. Median time between IBD diagnosis and occurrence of first EIM was 1 month (-37.5 – 149.0). 31 of the 55 patients (56.4%) were treated with one or more anti-TNF agents. IBD patients with EIM were more likely to be treated with anti-TNF compared to those without (56.4% vs. 35.0%, p=0.003). Response rates to anti-TNF depended on underlying EIM and were best for peripheral arthritis (61.5%) and uveitis (66.7%).

Conclusions: In a cohort of pediatric IBD patients, EIM were frequently encountered. In up to 30%, EIM appeared before IBD diagnosis. Knowledge of these findings might translate into an increased awareness of underlying IBD, thereby decreasing diagnostic delay. Anti- TNF for the treatment of certain EIM is effective although a substantial proportion of new EIM might present despite ongoing anti-TNF therapy.

Keywords: extraintestinal manifestations, inflammatory bowel disease, arthritis, uveitis, anti-TNF

What is known:

- Extraintestinal manifestations (EIM) are frequently observed in adult patients with inflammatory bowel disease (IBD)
- Little is known about EIM in the pediatric IBD population

What is new:

- EIM are common in pediatric patients with IBD
- Epidemiology and presentation of EIM seem to be similar in the pediatric and adult IBD population
- In up to 30% of those patients presenting with EIM, EIM appear before IBD diagnosis
- Type of EIM might affect the responses to anti-TNF. Best rates were seen for peripheral arthritis and uveitis

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic inflammatory disorders of the gastrointestinal tract and can be classified into the two main subtypes Crohn`s disease (CD) and ulcerative colitis (UC) (1). As IBD are systemic diseases, which can involve multiple organ systems, extraintestinal manifestations (EIM) are frequently observed affecting up to 50% of the adult IBD population (2-6). In a non-negligible proportion, EIM appear even before IBD diagnosis is established (7). While some reviews broaden the concept of EIM to non-IBD specific autoimmune disorders such as thyroid disease or vitiligo and IBD-related complications such as osteopathy or nephrolithiasis, the typical EIM involve the following four organs: skin (erythema nodosum (EN), pyoderma gangrenosum (PG), psoriasis, aphthous stomatitis), joints (peripheral arthritis, axial arthropathy), biliary tract (primary sclerosing cholangitis (PSC)) and eyes (uveitis) (7). Most of EIM parallel intestinal disease activity (8-12), are more common in CD than UC and are more frequently observed with longer IBD duration (13). In addition, up to one quarter presents with more than one EIM (8). Morbidity and mortality are considerably affected (14, 15). Although pathogenesis remains mostly elusive, intestinal and extraintestinal IBD seem to share TNF-dependent mechanisms (16) and several studies and case reports were able to demonstrate beneficial effect of anti-TNF treatments (17-23). However, EIM (such as arthritis and paradoxical psoriasiform reactions) can also resemble side effects of anti-TNF therapy (25).

While knowledge of prevalence, appearance and possible treatment options for EIM in adults is increasing, it is still limited in the pediatric IBD population. Recent studies have shown higher rates of EIM at IBD onset compared to adults with peripheral arthritis and aphthous stomatitis being the most prevalent (26, 27). To our knowledge, so far no study has addressed the

chronological order of EIM appearance in respect to IBD diagnosis or the influence of anti-TNF treatment on the evolution and development of EIM in a pediatric IBD cohort. Given this paucity of data, we aimed to assess the frequency and type of EIM, chronological order of appearance of EIM and the use of and response to anti-TNF treatment in the Pediatric Swiss IBD Cohort Study (PSIBDCS).

METHODS

Patients

The Pediatric Swiss IBD Cohort Study (PSIBDCS) is a nationwide sub-study of the Swiss IBD cohort study (SIBDCS) including all regions of Switzerland (28). Enrollment started in 2008. The SIBDCS and its sub-study are supported by the Swiss National Science Foundation and are approved by the local ethics committees of the participating centers. Patients are included in the PSIBDCS if they are 18 years old or younger. Additional inclusion criteria and regular assessment scheme (baseline and annual follow-up questionnaires) have been discussed elsewhere (29). Patients were recruited at University Hospitals, community hospitals and large private practices throughout Switzerland. A total of 329 pediatric patients are currently included. All 329 patients were retrospectively analyzed for the purpose of this study.

Definition of EIM and anti-TNF outcome

All EIM had to be diagnosed by clinical experts: Diagnosis of skin manifestations was established by a dermatologist, joint affections by a rheumatologist, eye manifestations by an ophthalmologist and PSC by a gastroenterologist. We analyzed the following EIM: peripheral arthritis, uveitis, PG, EN, aphthous stomatitis, axial arthropathy, psoriasis and PSC. Diagnosis of

EIM relied on previously published criteria (7, 26, 30). We did not consider anemia, glaucoma and pancreatic involvement as EIM because it may also be considered as complication of IBD therapy (26). Evolution of EIM under anti-TNF treatment was judged according to the physician`s global assessment, which was based on patient history and clinical findings. This anti-TNF response was classified into the following three categories: clinical improvement, stable disease course unaffected by anti-TNF treatment, and clinical worsening.

Data collection and management

Completed patient and physician questionnaires (baseline and annual follow-up) were sent to the datacenter of the SIBDCS located at the Institute of Social and Preventive Medicine, University of Lausanne, Switzerland, where data were validated by the responsible data manager and finally entered into a Microsoft Access database (Access 2000; Microsoft Switzerland Ltd. Liab. Co., Wallisellen, Switzerland). Baseline questionnaire at enrollment and annual follow-up questionnaires included demographic data, IBD subtype and diagnosis, disease localization according to international guidelines, prior and current medications as well as past and present EIM. Electronic and written charts of those patients, who reported past or present EIM, were additionally reviewed by clinical experts in order to extract exact appearance of EIM in relation to IBD diagnosis, EIM subtype, chronological order of appearance of multiple EIM and evolution of EIM in response to anti-TNF treatment. All 329 patients in the PSIBDCS were eligible. For detailed analysis, only those patients with one or more EIM were included. For a comparison between the pediatric and adult population, data from the SIBDCS was used according to a recent study conducted by Vavricka et al (7).

Statistical analysis

For all statistical analyses, IBM software SPSS version 23.0.0 (2014 SPSS Science, Inc., Armonk NY) was used. Metric data are shown as medians with their total range. Categorical data are depicted as percentage of the group total. Comparison between categorical variables was performed by using Chi-square test or Fisher`s exact test, if sample size was low ($n<10$). A two sided p-value of <0.05 was considered statistically significant. The association between potential predicting factors and positive anti-TNF outcome was analyzed by means of logistic regression.

RESULTS

Patient demographics

Of the 329 pediatric IBD patients included in the study, 173 (52.6%) had CD and 156 (47.4%) had UC/IBD-U, 148 patients were female (45.0%). Median age at enrollment was 14 years (0-17) and median age at IBD diagnosis was 12 years (0-16). The patients had been suffering from IBD for a median of 3 years (0-16). Patient demographics according to IBD subtype (including disease localization and received medications) are summarized in **Table 1**. Of the 329 patients, 55 presented with one or more EIM (16.7%). The characteristics of those patients are depicted in **Table 2**.

Frequency and types of EIM

Of the 55 patients with at least one EIM, 39 patients had CD (39/55, 70.9%), 12 patients UC (12/55, 21.8%) and 4 patients IBD-U (4/55, 7.3%) as their underlying condition. Of these 55 EIM patients, 39 (70.9%), 12 (21.8%), three (5.5%) and one patient (1.8%) reported one, two, three and four EIM, respectively. At IBD onset, presence of EIM was more frequent than in the

adult population (28/329, 8.5% vs. 62/1249, 5.0%, p=0.014). EIM were more frequently observed in CD patients (39/173, 22.5%) when compared to UC/IBD-U patients (16/156, 10.3%, p=0.003). The most prevalent EIM were peripheral arthritis (26/329, 7.9%) and aphthous stomatitis (24/329, 7.3%), followed by uveitis (6/329, 1.8%), EN (5/329, 1.5%), axial arthropathy (5/329, 1.5%), psoriasis (4/329, 1.2%), PSC (4/329, 1.2%) and PG (2/329, 0.6%). Peripheral arthritis, axial athropathy and EN were less frequently encountered among pediatric IBD patients compared to adult patients (7.9 vs. 20.5%, p<0.001, 1.5 vs. 4.8%, p=0.008 and 1.5 vs. 3.7%, p=0.048). Frequency of other EIM were comparable between the two populations. For a detailed overview see **Figure 1**. While 27.6% of all EIM (21/76) appeared before the diagnosis of IBD, the majority of EIM appeared once IBD diagnosis was established (42/76, 55.3%). The remaining proportion of EIM (12/76, 15.8%) was first observed at the time of establishment of IBD diagnosis. Data from 1 EIM was missing. So, at the time of IBD diagnosis, 28 of the 55 patients presented with a total of 33 EIM (observed before or at the time of IBD diagnosis); Aphthous stomatitis and peripheral arthritis were again the most frequently observed EIM (15/28, 53.6% and 10/28, 35.7%, respectively). For a synopsis over the phenotypic features at IBD diagnosis see **Supplemental Digital Content 1, Table 1** (*http://links.lww.com/MPG/A827*). Details about frequency and type of EIM according to IBD subtype are shown in **Table 2.**

Distribution of different EIM according to their chronological appearance

Aphthous stomatitis was the most prevalent EIM (21/55, 38.2%), which appeared as first EIM (n=55), followed by peripheral arthritis (19/55, 34.5%) and uveitis (4/55, 7.3%). If the patient was diagnosed with a second EIM (n=16), peripheral arthritis (5/16, 31.3%), EN (3/16, 18.8%), aphthous stomatitis (2/16, 12.5%) and axial arthropathy (2/16, 12.5%) were most frequent. In

those patients presenting with a third EIM (n=4), occurrence of the following EIM were reported: peripheral arthritis (1/4, 25.0%), uveitis (1/4, 25.0%), aphthous stomatitis (1/4, 25.0%) and psoriasis (1/4, 25.0%). Median time between IBD diagnosis and occurrence of first EIM was 1 month (range -37.5 – 149.0). **Figure 2** illustrates the chronological order of appearance of each individual EIM in relation to the time of IBD diagnosis (in months). Peripheral arthritis appeared before IBD diagnosis in 28.0% (7/25, exact appearance in 1 case unknown), uveitis in 16.7% (1/6), EN in 20% (1/5), axial arthropathy in 40.0% (2/5) and aphthous stomatitis in 29.2% (7/24). All cases of psoriasis (4/4, 100%) and PG (2/2, 100%) appeared after IBD diagnosis was established. In addition, peripheral arthritis (64.0 vs. 28.0%, p=0.011) and uveitis (83.3 vs. 16.7%, p=0.021) were significantly more likely to appear after diagnosis of IBD than before establishment of IBD diagnosis. Median lag of time of appearance prior to IBD diagnosis in the group of patients in whom EIM preceded IBD diagnosis was -5.0 months (range -37.5 to -0.4)

Type of anti-TNF treatment and treated EIM

Anti-TNF therapy was initiated in 31 of the 55 patients with EIM (56.4%). Most of them were treated with a single anti-TNF agent (23/31, 74.2%), while five patients were treated with two and three patients with three different anti-TNF agents (5/31, 16.1% and 3/31, 9.7%, respectively). So, a total of 42 treatment courses were initiated. In 78.6% (33/42), anti-TNF treatment was started for the purpose of treating underlying IBD activity. In 3 cases (3/42, 7.1%), anti-TNF was solely initiated for the purpose of treating EIM; Infliximab was started for peripheral arthritis (n=1) and axial arthropathy (n=1), adalimumab was initiated for peripheral arthritis (n=1). In five cases (5/42, 11.9%), anti-TNF was started for the purpose of treating both intestinal disease activity and EIM. In 1 case, exact indication for anti-TNF treatment was not

known. IBD patients presenting with EIM were more likely to be treated with anti-TNF compared to those without EIM (31/55, 56.4% vs. 96/274, 35.0%, p=0.003). The most frequently treated EIM were peripheral arthritis (16/42, 38.1%) and aphthous stomatitis (13/42, 31.0%), followed by axial arthropathy, uveitis and EN. For details see **Table 3**. Under anti-TNF treatment, 23 EIM appeared in 19 of the 31 treated patients (19/31, 61.3%). Among those 23 EIM, peripheral arthritis (6 cases) and aphthous stomatitis (5 cases) were the most frequently reported. Three cases of psoriasis occurred under anti-TNF therapy, which can be considered as anti-TNF induced psoriasiform skin lesions. Further reported EIM, which appeared under anti-TNF, were: uveitis (2 cases), PG (1 case), EN (2 cases) and axial arthropathy (1 case). In remaining three cases, the exact EIM subtype was unknown.

Clinical evolution of EIM under anti-TNF treatment

Data on clinical outcome of anti-TNF treatment was available for 37 of the 53 treated EIM (69.8%). In the majority, EIM showed improvement (17/37, 45.9%) or stable disease course (13/37, 35.1%), while clinical worsening was observed in only 7 cases (7/37, 18.9%). Peripheral arthritis and uveitis showed good clinical response rates to anti-TNF (61.5% and 66.7%, respectively), while those of PG, axial arthropathy, aphthous stomatitis and EN were ≤50% (50.0%, 50.0%, 33.3%, and 33.3%, respectively, **Table 3**). In a multivariate regression model adjusted for age and gender, appearance of EIM before IBD diagnosis was the only independent predictor for positive anti-TNF outcome (OR 9.70, 95% confidence interval 1.04-90.04, p=0.046). Details about the multivariate analysis can be found in the **Supplemental Digital Content 2, Table 2** (*http://links.lww.com/MPG/A828*).

DISCUSSION

In this analysis of the Pediatric Swiss IBD cohort study, we report on frequency and chronological order of appearance of extraintestinal manifestations, the use of anti-TNF agents, and the disease course under such therapy. EIM are common in pediatric patients with IBD and can appear in nearly 30% before IBD diagnosis is established. Anti-TNF are used frequently in those patients, although they are started for the purpose of treating EIM in only a minority. Type of EIM might affect anti-TNF outcome. Best response rates were seen for peripheral arthritis and uveitis.

EIM were frequently encountered in pediatric IBD, the prevalence of 16.7% is comparable to prior data from Guariso et al (27). However, prevalence is considerably lower compared to the studies conducted by Dotson (30) and Heyman (26), which is mainly due to our more stringent definition of EIM, as we did not include non-specific arthralgia or other non-specific EIM such as anemia, hepatitis, pancreatitis or osteoporosis. In accordance to the findings of Guariso et al., presence of EIM at IBD onset was more frequent in the PSIBDCS compared to the adult population (8.5 vs. 5%), although difference was considerably smaller (14.3 vs. 7.3% in the study of Guariso) (27). Our numbers fit well within the range of 6-47% EIM prevalence typically reported (2, 4-6, 13, 31). Our finding that EIM were more frequently observed in CD compared to UC patients is consistent with prior studies from adult IBD cohorts (7, 8, 13). Moreover, the order of frequency is consistent throughout the adult EIM literature and our data are in agreement with published observations: Musculoskeletal symptoms (such as peripheral arthritis) are followed by stomatitis, ophthalmological problems (such as uveitis), and skin changes (8, 26). Although the proportion of patients presenting with arthritis is higher among adult patients,

order of frequency of EIM did not show a difference between the adult and pediatric IBD patients. EIM were more likely to appear after IBD diagnosis compared to before. Nonetheless, a non-negligible proportion (up to 30%) of EIM appeared before IBD diagnosis was established. Axial arthropathy appeared before IBD diagnosis in an even higher proportion. Both findings are consistent with data from adult cohorts (7). So, clinicians should be aware of those EIM manifesting before intestinal symptoms in order to decrease the diagnostic delay. Our group has recently shown that such diagnostic delay is a concern (32) and that a delayed diagnosis is associated with a complicated disease course in CD patients (33). Appearance of more than one EIM was observed only infrequently. Thus, the fact, that one EIM seems to increase the susceptibility of developing other EIM does not seem to be true for pediatric patients (34) or latency between first and second EIM may have been too long to allow detection in children. Taken together, our data suggest that epidemiology and presentation of EIM is quite similar in the pediatric and the adult population, suggesting similar disease mechanisms.

Anti-TNF were frequently used in pediatric patients with EIM. However, those agents were specifically initiated for treating EIM in only a minority. So, clinical practice seems to be in accordance to current guidelines, which recommend to treat underlying IBD activity rather than EIM themselves. Nonetheless, patients with EIM were significantly more often treated with anti-TNF than those without EIM. The latter may be explained by prior findings from Vavricka et al. who showed that active disease is an independent risk factor for EIM in both UC and CD (8). Upon anti-TNF treatment, EIM showed overall response rates of nearly 50%, which depended on the underlying EIM with the best rates for peripheral arthritis and uveitis. While direct comparisons are not possible, higher response rates to anti-TNF treatment were described in the

adult population (71.8%) (35). New onset of EIM under anti-TNF treatment also has been encountered in our study. Diagnosis of psoriasis was established in 3 of the 31 anti-TNF treated patients, which can be interpreted retrospectively as anti-TNF induced psoriasiform skin lesion. Prevalence seems to be in accordance to that reported in the literature (36).

Our study has several strengths and some limitations as well. So far, it is one of the largest analyses of collected data evaluating frequency and occurrence of EIM in the pediatric IBD population. Furthermore, a detailed chart review revealed information about chronological appearance of EIM according to EIM subtype, the use of anti-TNF treatment and clinical response to such a therapy. The combination of physician and patient based questionnaire might have prevented the underreporting of EIM in our study population. However, we used an uncontrolled, non-interventional study design, which limits interpretation of anti-TNF treatment outcome. With annual follow-up visits, important details occurring during this period of time might have been missed. However, this potential recall bias has been limited by the combination of physician- and patient-based questionnaires. Given the fact that the Pediatric Swiss IBD cohort is not strictly population based, a selection bias may be present. For instance, patients included by private practices and community hospitals were underrepresented compared with those patients included by university hospitals (30.9% of the patients presenting with EIM were recruited in private practices or community hospitals, while 69.1% were recruited by physicians working in a university hospital). A clear limitation of our analysis is that – at the time of data analysis – we did not clearly differentiate between psoriasis and psoriasiform anti-TNF associated skin lesions, which is an increasingly reported phenomenon (36). However, with 4 cases, prevalence of psoriasis was extremely low, and 3 out of 4 cases can be retrospectively

considered as anti-TNF induced as they presented under anti-TNF treatment for the first time. Due to the retrospective nature of the study, a non-negligible proportion of patients received concomitant immunomodulators and/or steroids in addition to anti-TNF, which may have led to an overestimation of anti-TNF response rates.

In summary, in a cohort of pediatric IBD patients, EIM were frequently encountered. In up to 30% of patients, EIM appeared before IBD was diagnosed. Knowledge of these findings may result in increased awareness of underlying IBD, thereby decreasing potential diagnostic delay. Anti- TNF for the treatment of certain EIMs is effective although a substantial proportion of new EIMs might present despite ongoing anti-TNF therapy. However randomized controlled trials are needed in the pediatric IBD population.

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	CD patients	UC/IBD-U patients	All IBD patients
Number of patients	173 (52.6)	156 (47.4)	329 (100.0)
Gender			
Male	104 (60.1)	77 (49.4)	181 (55.0)
Female	69 (39.9)	79 (50.6)	148 (45.0)
Age at diagnosis in years	12, 10-14	11, 7-14	12, 9-14
(median, IQR, range)	0-16	0-16	0-16
Age at enrollment [years]	14, 12-15	13, 11-15	14, 11-15
(median, IQR, range)	0-17	0-17	0-17
Age at latest follow-up [years]	16, 14-17	16, 13-17	16, 13-17
(median, IQR, range)	0-18	0-18	0-18
Disease duration [years]	3, 2-5	3, 1-6	3, 2-5
(median, IQR, range)	0-15	0-16	0-16
Diagnostic Delay [months]	4.1, 2.0-8.1	3.0, 1.0-6.1	3.1, 2.0-7.1
(median, IQR, range)	0-83.2	0-59.9	0-83.2
Initial Disease Location [CD]			
L1	23 (13.3)	-	
L2	22 (12.7)	-	
L3	119 (68.8)	-	
L4 only	3 (1.7)	-	
Unknown/unclear	6 (3.5)	-	
Initial Disease Location [UC]			
E1	-	13 (8.3)	
E2	-	28 (18.0)	
E3/E4	-	104 (66.7)	
Unknown/unclear	-	11 (7.0)	
Fistulas			
Perianal Fistula	24 (13.9)	-	
Other Fistula	12 (6.9)	-	
Stenosis			
Any stenosis	22 (12.7)	-	
Medication Ever Received			
5-ASA	84 (48.6)	149 (95.5)	233 (70.8)
Antibiotics	64 (37.0)	46 (29.5)	110 (33.4)
Steroids	140 (80.9)	117 (75.0)	257 (78.1)
Immunomodulators	155 (89.6)	101 (64.7)	256 (77.8)
Anti-TNF	87 (50.3)	40 (25.6)	127 (38.6)

TABLE 1: Patient demographics of the Pediatric Cohort

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	All n=55 (%)	UC n=12 (%)	CD n=39 (%)	IBD-U n=4 (%)
Sex				
- **male**	34 (61.8)	6 (50.0)	26 (66.7)	2 (50.0)
- **female**	21 (38.2)	6 (50.0)	13 (33.3)	2 (50.0)
Age at IBD Diagnosis in years	11.3 (0.8-15.7)	9.5 (2.5-15.5)	11.5 (0.8-15.4)	14.0 (12.4-15.7)
Number of EIM				
- 1	39 (70.9)	6 (50.0)	29 (74.4)	4 (100.0)
- 2	12 (21.8)	6 (50.0)	6 (15.4)	0 (0.0)
- 3	3 (5.5)	0 (0.0)	3 (7.7)	0 (0.0)
- 4	1 (1.8)	0 (0.0)	1 (2.6)	0 (0.0)
Age at first EIM in years	12.8 (3.1-17.4)	11.5 (3.8-15.4)	13.1 (3.1-17.4)	13.0 (9.3-14.9)
Time from IBD to first EIM in months	1.0 (-37.5-149.0)	5.0(-26.0-149.0)	1.5 (-28.0-102.0)	-18.0 (-37.4-1.0)
Type of EIM				
- Arthritis	26 (47.3)	6 (50.0)	19 (48.7)	1 (25.0)
- Uveitis	6 (10.9)	0 (0.0)	5 (12.8)	1 (25.0)
- PG	2 (3.6)	1 (8.3)	1 (2.6)	0 (0.0)
- EN	5 (9.1)	1 (8.3)	4 (10.3)	0 (0.0)
- Stomatitis	24 (43.6)	5 (41.7)	18 (46.2)	1 (25.0)
- AS	5 (9.1)	2 (16.7)	3 (7.7)	0 (0.0)
- PSC	4 (7.3)	3 (25.0)	0 (0.0)	1 (25.0)
- Psoriasis	4 (7.3)	0 (0.0)	4 (10.3)	0 (0.0)
Occurrence of EIM	**n=76**	**n=18**	**n=54**	**n=4**
- Before	21 (27.6)	4 (22.2)	14 (25.9)	3 (75.0)
- Concomitant	12 (15.8)	3 (16.7)	9 (16.7)	0 (0.0)
- After	42 (55.3)	11 (61.1)	30 (55.6)	1 (25.0)
- Unknown	1 (1.3)	0 (0.0)	1 (1.9)	0 (0.0)

TABLE 2: Demographics and frequency and type of EIM according to IBD subtype. AS, axial arthropathy; EN, erythema nodosum; PG, pyoderma gangrenosum; PSC, primary sclerosing cholangitis

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	All anti-TNF (n=42)
Indication for anti-TNF	
- IBD	33 (78.6)
- EIM	3 (7.1)
- Both	5 (11.9)
- Unknown	1 (2.4)
Treated EIM	
- Arthritis	16 (38.1)
- Uveitis	4 (9.5)
- PG	3 (7.1)
- EN	4 (9.5)
- Stomatitis	13 (31.0)
- AS	5 (11.9)
- PSC	0 (0.0)
- (Unknown type)	(8)
Outcome of treated EIM	**n=37**
- Improvement	17 (45.9)
- Stable disease	13 (35.1)
- Worsening	7 (18.9)
- (unknown outcome)	(16)
Anti-TNF response rates	
- Arthritis	61.5% (8/13)
- Uveitis	66.7% (2/3)
- PG	50.0% (1/2)
- EN	33.3% (1/3)
- Stomatitis	33.3% (3/9)
- AS	50.0% (2/4)

TABLE 3: Anti-TNF treatment. AS, axial arthropathy; EN, erythema nodosum; PG, pyoderma gangrenosum; PSC, primary sclerosing cholangitis

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FIGURE 1: Frequency of EIM subtype among those patients presenting with EIM according to IBD cohort study (adult vs. pediatric). EN, erythema nodosum; PG, pyoderma gangrenosum; PIBDCS, Pediatric Swiss IBD Cohort Study; PSC, primary sclerosing cholangitis; SIBDCS, Swiss IBD Cohort Study.

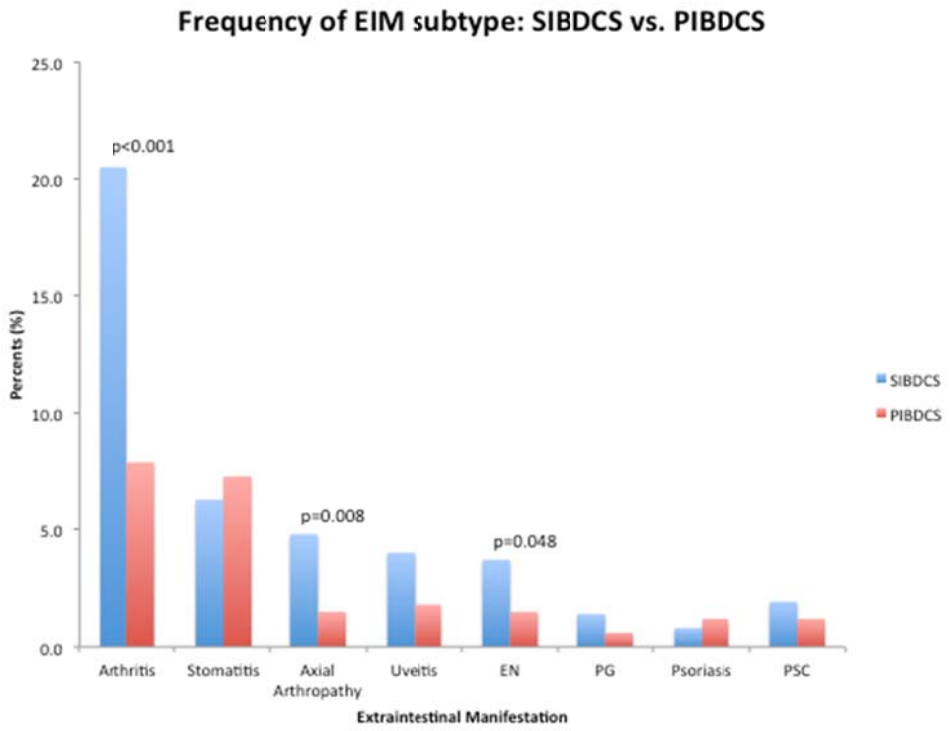

FIGURE 2: Chronological order of appearance of EIM in relation to the time of IBD diagnosis. Data are presented as horizontal boxplots. The box comprises the 25th and 75% percentile; the vertical line in the box corresponds to the median. AS, axial arthropathy; EN, erythema nodosum; PG, pyoderma gangrenosum; PSC, primary sclerosing cholangitis.